



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**Note to Reader**

**Background:** As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply.

EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

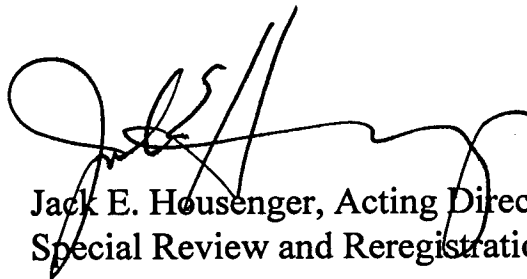
The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

**Note:** This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket ( RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

A handwritten signature in black ink, appearing to read 'J. Housenger', is written over the typed name and title.

Jack E. Housenger, Acting Director  
Special Review and Reregistration Division

282

MEMORANDUM

DATE: January 23, 1995

TO: Bruce Kitchens  
Occupational and Residential Exposure Branch

THRU: Francis B. Suhre, Acting Section Head  
Registration and Special Review Section  
  
and  
  
Jerome Blondell, Ph.D., M.P.H.  
Registration and Special Review Section

FROM: Virginia Dobozy, V.M.D., M.P.H.

SUBJECT: Analysis of Chlorpyrifos IDS Data for Domestic Animals

**SUMMARY AND RECOMMENDATIONS**

The incidents of adverse reactions reported to the Incident Data System for domestic animals exposed to chlorpyrifos were tabulated and analyzed. Incidents in dogs and cats were categorized as follows: 1) cats exposed by direct application (e.g. collars, dips, etc.); 2) cats exposed by premise application; 3) dogs exposed by direct application; and 4) dogs exposed by premise application. The analysis demonstrated misuse of the chemical in cats. Although chlorpyrifos is registered only for flea collars on cats, 59% of the total number of incidents involving domestic animals were in cats. Of those cats exposed to products registered only for use on dogs, mainly dips, 30% died. The analysis also demonstrated that there is misuse of premise treatment products, including practices such as applying these products directly to animals and not removing pets from premises during application. In a total of 107 incidents of premise application involving cats, 26 (24%) were due to misuse. The findings of the analysis agree with data reported in the veterinary literature, especially that from the National Animal Poison Control Center.

OPP has recently proposed label revisions for all pet pesticide products. However, it is unlikely that these revisions will alter the patterns of misuse in cats. The options for reducing the risk of serious injury and death in cats due to direct chlorpyrifos exposure are few. Although most products registered for use on dogs contain warnings to not use on cats, there is evidence from IDS reports and the veterinary literature that the instructions are not being followed. Given that there are less toxic alternatives to chlorpyrifos for use in cats and the trend in flea control is to preventive rather than treatment methods, a cancelation of all chlorpyrifos products for direct application to dogs and cats, except flea collars, should be considered. Methods of risk mitigation for premise application products should be explored to guarantee that animals are not present during treatment and such products are not applied directly to animals. In addition, the amount of time required before safely reintroducing animals into a treated area should be re-examined.

## DATA BASE

Incident data reported to IDS involving domestic animal exposure to chlorpyrifos were analyzed.

## RESULTS

Total Number of Incidents in Analysis = 277

Total Number of Incidents Involving Cats (%) = 164 (59%)

Total Number of Incidents Involving Dogs (%) = 94 (34%)

Total Number of Incidents Involving Other Domestic Animals = 22 (8%)<sup>1</sup>

Incidents involving exposure to dogs and cats were further analyzed separately by type of exposure, either by direct application to the animal or by indirect exposure via premise application of products.

### Cats - Direct Application

A total of 57 incidents involving direct application of chlorpyrifos to cats were categorized as to the type of adverse reaction. Although the chemical is registered for use on cats solely in the form of collars, only 6 incidents in 6 cats of adverse reactions involving collars were reported. The remaining 51 incidents involving 91 cats resulted from misuse of dips and sprays, with death reported in 27 cases (30%).

### Cats - Premise Application

A total of 107 incidents involving exposure to 158 cats via premise treatment were analyzed. Death was reported in 29 (18%) of cats. Of those, 26 incidents (24%) involving 37 cats resulted from misuse in which the cat was not removed from the house during treatment by the owner or pest control operator or a product registered for premise treatment was applied directly to the cat.

### Dogs - Direct Application

A total of 32 incidents involving direct application of chlorpyrifos to 45 dogs were analyzed. Two incidents involved misuse in which puppies younger than the cut-off age on the label were treated. Death occurred in one incident; one puppy of a litter of eight 2-3 week-old Rottweillers died. Four incidents in 6

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<sup>1</sup> Three incidents involved exposure to both dogs and cats. They were counted for both species and thus the sum of the individual categories exceeds the total number of incidents.

animals involved flea collars. Death was reported in a total of 14 dogs (31%) (including the Rottweiler puppy). The type of products involved with the deaths included dips (9 cases); sprays and collars (2 cases, each) and shampoos (1 case).

#### Dogs - Premise Application

A total of 62 incidents involving exposure to 94 dogs via premise treatments were analyzed. Three (3) incidents involved misuse in which either the dog was not removed from the house during treatment, the product was improperly diluted or the dog was maliciously exposed to the product. Death was reported in 33 animals (35%), the majority in puppies (a total of 25 puppies in 4 litters).

These data and the categories of adverse reactions reported are presented in Table 1.

Table 1: Chlorpyrifos Incident Data in Domestic Animals - Type of Adverse Effect in Dogs and Cats - Number of Animals Affected\*

	Type of Adverse Effect**										
	Death/ Euthanasia	OP Signs	Neuro Signs	GI Signs	General Systemic Signs	Dermal Signs	Resp Signs	Urinary Signs	Allergic Reaction	Ocular Signs	Sal. Only
<b>Cats - Direct Exposure (n=97)</b>											
Collars	1		1	4	1	2					
Misuse	27	41	18		10		1				
<b>Cats - Premise Exposure (n=158)</b>											
	29	106	11	12	15		10	3			4
<b>Dogs - Direct Exposure (n=45)</b>											
Collars	2					2			2		3
Other	12	7	9	10	2	1					
<b>Dogs - Premise Exposure (n=94)</b>											
	33***	29****	5	25	7	2	3			2	

\* Multiple signs may be reported for each animal.

\*\* OP Signs = combination of gastrointestinal & neurological signs; Neuro Signs = neurological signs only;

GI Signs = gastrointestinal signs; General Systemic Signs = includes nonspecific signs such as lethargy and anorexia; Allergic Reaction = report indicates that animal may have been hypersensitive/allergic to product

\*\*\* Includes a total of 25 puppies in four litters.

\*\*\*\* Includes 2 cases in which the report indicates that the cholinesterase level was depressed but the type of signs observed were not presented

## **USE INFORMATION**

Use information on chlorpyrifos comes from the National Home and Garden Pesticide Use Survey, March 1992. It was estimated that 1,467,000 containers of the chlorpyrifos marketed in 1990 was used in the treatment of dogs, cats or kennels. This was 5.60% of the household market for the chemical and 2.85% of all chemicals used to treat cats, dogs and kennels.

## **DATA LIMITATIONS**

1. Any calculations should only be considered estimates due to the differences in the usefulness of individual IDS reports, as discussed in item number 2.

2. This analysis was conducted without regard to the certainty index assigned to each incident report. When reviewed by HED, incidents are categorized as to the likelihood that the pesticide contributed to the adverse effect, using the following categories: definite, probable, possible, unlikely, unrelated and unknown. The validity and usefulness of such categorization is often restricted by the amount of information provided in the incident reports. (There are no mandatory data elements which must be included.) The type of information provided by different registrants varies from simple statements of the final outcome of an event to detailed descriptions of exposure, symptoms, treatment and outcome. Some registrants have contracts with the National Animal Poison Control Center (NAPCC). This organization answers telephone calls from pet owners and veterinarians regarding all types of poisonings. Through inquiries about exposure, signs and diagnoses, the veterinary toxicologists fielding the calls can prepare detailed reports and adequately categorize cases. However, those registrants that do not use the NAPCC often submit incident reports that are brief and cryptic. This lack of information for some cases prevents adequate categorization.

3. There is an under-reporting of pesticide incidents. It is reasonable to assume that some registrants have failed to report adverse effects, given that incidents are received for some products but not others containing similar active ingredients. In addition, the consumer may be unaware of a mechanism for reporting an incident to the registrant or EPA. Therefore, any estimate of potential risk to domestic animals identified by this analysis is probably less than actually exists. The analysis does confirm risks which have been cited in the veterinary literature. (See Literature Review.)

4. Realistic ratios of the number of incident reports to the amount



of product used cannot be made. As stated previously, there is an under-reporting of incidents. Second, there is some use information for chlorpyrifos, as presented above, but it has limited applicability for calculating such ratios. The number of containers sold is not a good estimate of the number of animals exposed because multiple animals may be treated with the same container. In addition, analyses of incident data on domestic animals for other chemicals, for which to compare the chlorpyrifos analysis, have not been done in the past.

### **CONCLUSIONS FROM ANALYSIS**

The following conclusions can be drawn from a tabulation of the incident data on domestic animals:

1. Misuse of chlorpyrifos-containing pet products occurs in animals. Treatment of cats with products, especially sprays and dips, registered only for use on dogs occurs frequently.
2. Cats are at risk of life-threatening consequences if treated with chlorpyrifos sprays and dips; in 51 incidents, 27 of 91 cats (30%) died.
3. There is evidence that cats and dogs, to a lesser degree, are at risk from exposure to chlorpyrifos during premise treatment. A significant factor in this risk is misuse. Twenty-six (26) of 107 incidents involving 37 cats resulted when the animal was either not removed from the premise during treatment or else the product was applied directly to the animal. Three (3) of 62 incidents involving dogs resulted when the animal was either not removed from the premise, the product was improperly diluted or the animal was maliciously exposed to the product.

### **LITERATURE REVIEW**

The veterinary literature confirms the conclusions of the above analysis. In 1984, the NAPCC (NAPCC) received almost 8,000 calls regarding poisonings in small animals.<sup>1</sup> A total of 745 calls in dogs and 515 in cats involved insecticides, more than any other class of toxicant. Approximately one-third were judged to be definite toxicosis and one-fifth suspected toxicosis (categories: toxicosis, suspected toxicosis, doubtful toxicosis, information only). Data on specific chemicals were not supplied at that time. However, this article did note that toxicosis and sometimes death results when products intended for dogs, especially dip solutions, are used on cats.

In 1986, insecticides, as a category, ranked as the third highest

number of calls for dogs (1771 calls) and the first for cats (1303) received by the NAPCC.<sup>2</sup> Of these calls, 12.8 in dogs and 25.7% in cats were judged to be toxicoses. The number of calls concerning chlorpyrifos was 115 for dogs and 184 for cats.

In 1987, the NAPCC reported 25 deaths from chlorpyrifos in cats and two in dogs. This number of deaths in cats was more than from any other generic chemical.<sup>2</sup> (Detailed information on the number of calls involving insecticides, chlorpyrifos, etc. was not provided in the literature article.)

In 1988, the NAPCC received 168 calls about cats and 238 about dogs exposed to chlorpyrifos.<sup>3</sup> The percentage of calls assessed as toxicosis or suspected toxicosis was 61% and 28% in cats and dogs, respectively.

The American Association of Poison Control Centers reported receiving 41,854 animal poisoning calls in 1990.<sup>4</sup> It was estimated that 75% of calls involved dogs, 20% cats and 4% other pets. (Data on species of animal are not recorded.) Of all calls in animals, 75% involved exposure to non-drug products; 19% of all calls involved insecticides with death being reported in 94 animals. Three types of products were most commonly responsible for death: ethylene glycol (9.6%), anticoagulant rodenticides (9.2%) and organophosphorus insecticides (7.3%).

The clinical signs and time to onset of chlorpyrifos toxicity in the cat sometimes are not typical of organophosphate poisoning. This may lead to misdiagnosis by veterinarians and consequently under-reporting of adverse effects. The onset of clinical signs may be delayed 1-5 days following topical exposure and may be more subtle and non-specific, such as anorexia and behavioral aberrations.<sup>2,3</sup> After oral exposure through direct ingestion or grooming, the result may be more rapid. The predominant neurological signs are tremors (especially in the muscles of the back, neck and top of head), ataxia and seizures. Non-specific neurological signs, such as mental depression and anorexia, may persist for 2-4 weeks. Changes in personality, hyperesthesia and hyperactivity may also be observed. Gastrointestinal signs include salivation, diarrhea and vomiting. Pulmonary effects are related to bronchiolar constriction and hypersecretion which lead to tachypnea and dyspnea. In a study of acute oral toxicity, 10 mg/kg of the chemical did not induce clinical signs of toxicity, but death occurred in 1 of 12 cats at 40 mg/kg.<sup>5</sup>

The cat is also one of the species most sensitive to the delayed neurotoxic effects of chlorpyrifos, along with the human, chicken, calf, pig, lamb and rabbit.<sup>6</sup> The species which are most resistant are the rat, dog and monkey. In an experimental study, 300 mg/kg of

chlorpyrifos intramuscularly in cats produced delayed neurotoxicity after 19 days.<sup>7</sup> Two cases of naturally-occurring chronic toxicity in cats have been reported.<sup>8</sup> Both cats lived in an apartment that was sprayed for fleas six times (every 3 days) during an 18-day period. The cats were not allowed in the apartment for approximately 2-3 hours during the days of the spraying but were then reintroduced. The first cat became anorexic and developed personality changes after four applications of chlorpyrifos. Approximately four days later, it became paraparetic in the pelvic limbs, had generalized hyperesthesia and bilateral dilated pupils. The second cat was presented to the veterinary hospital one week after the first. On physical exam, it was noted to have bilateral dilated pupils, generalized hyperesthesia and severe pelvic limb paresis. A dog that lived in the same apartment was unaffected. Both cats had decreased cholinesterase activity and abnormal electromyograms. The neurological signs in both resolved rapidly after treatment with 2-PAM and atropine. Muscle weakness leading to total loss of voluntary motor function may have lead to the clinical signs observed. This rapid recovery is not consistent with the degeneration of axons seen in delayed peripheral neuropathy.

At a recent meeting of the D.C. Academy of Veterinary Medicine, Dr. Cheryl Chrisman of the University of Florida played a videotape of a cat with generalized paresis as a result of chlorpyrifos exposure during a premise application.<sup>9</sup> The owner's apartment had been sprayed one week prior to the onset of the paresis. The cat also displayed a strange ventral neck flexion. Dr. Val Beasley of the University of Illinois indicated that this type of abnormal positioning was also seen in the experimental cats with delayed neuropathy.<sup>10</sup>

Recent or current administration of several categories of drugs may potentially increase an animals's susceptibility to organophosphate toxicity.<sup>11</sup> The categories include certain inhalant anesthetics, tranquilizers and antibiotics. Veterinarians may delay surgery or avoid inhalant anesthetics if an animal is exposed to multiple cholinesterase-inhibiting chemicals.

Offering advice on flea control occupies a major portion of a veterinarian's professional time. In a survey of 42,000 households, one-third reported that flea control was the reason for visiting a veterinarian.<sup>12</sup> In the Southeast United States, flea-related diseases account for 50% of dermatological cases referred to veterinarians. The veterinary literature warns practitioners of the dangers of exposure of pets, especially cats, to cholinesterase-inhibiting pesticides. Veterinarians at the NAPCC have been especially concerned with the use of chlorpyrifos. In the 1984 report, they warned that more often toxicosis and sometimes death results when products intended for dogs, especially dip solutions,

are used on cats.<sup>1</sup> Dr. Beasley of the NAPCC has written, "In hindsight, it should have been predicted that persons who have recently dipped their dogs are also likely to dip their cats without rereading the label or recalling precautions against other uses of such products. A simple solution to this problem would be to abandon such formulations voluntarily or through regulation."<sup>13</sup> Dr. William Buck, also of the NAPCC, has stated, "...chlorpyrifos probably can be safely used in the house and on lawn areas to which cats have access, provided that its application does not result in significant exposure to the cats. To accomplish this, one should make certain that a liquid chlorpyrifos formulation applied to the premise has completely dried or that a powder chlorpyrifos formulation is not picked up on the cats' feet, only to be licked off by them. Cats probably should not be placed in an area to which chlorpyrifos has been applied on the same day."<sup>14</sup>

#### **HUMAN EXPOSURE VIA PET PRODUCTS**

The state of California recently notified EPA that it is considering placing all pesticide products formulated as dips and shampoos for use on dogs and cats into its reevaluation process.<sup>15</sup> The reason for the concern is the number of illnesses by applicators as a result of being dermally exposed to these products. At issue is the lack of precautionary statements on the label requiring the use of gloves or goggles. From 1982 through 1990, 71 illnesses associated with pet products were reported. The majority involved sprays (30 cases) and dips (25 cases). A large proportion of the sprays were antimicrobials and are sprays not applied to animals. Four active ingredients accounted for 60% of the total cases - phosmet, pyrethrins/PBO, sodium hypochlorite and D-limonene. There were four cases involving chlorpyrifos. The Department of Pesticide Regulation indicated that it suspects the number of illnesses is greatly under-reported in this particular group of users.

#### **PR NOTICE FOR PET PRODUCTS**

On September 15, 1994, the Registration Division published the availability of a draft PR notice which would require registrants of pet pesticide products to revise their labeling. A copy is attached. The basis for this requirement were reports of adverse effects to IDS, mostly in dogs and cats, but also in humans following exposure to such products. The labeling revision would include additional use directions and precautions to ensure that the products are used safely. The PR notice required that products registered for dogs only would contain the following statement, "DO NOT USE ON CATS or other animals." Many registrants objected to the

implementation of these changes. On August 31, 1995, the Chemical Specialties Manufacturers Association (CMSA) responded with suggestions for compromise on the label revisions. They suggested that the above statement in quotations be replaced by, "Use Only On (Dogs, Cats, etc.)". The value of this revision in reducing the chlorpyrifos risk in cats is questionable. A review of the labels of some chlorpyrifos products for direct application to dogs showed that the vast majority already contain such instruction. Of 10 products listed in *Veterinary Pharmaceuticals and Biologicals, 8th Edition*, 9 state either in capital or small case letters, "Do not use on cats."<sup>16</sup> A workgroup within OPP is in the process of developing a consensus response to the CMSA proposal.

**FUTURE OF FLEA CONTROL**

A recent article in the *Journal of the American Veterinary Medical Association* discussed the future of flea control with several veterinarians expert in the field.<sup>17</sup> Their opinion was that the focus of flea control is changing from treatment to prevention and from using chemicals to "natural" means of control. New products recently marketed include an insect development inhibitor (IDI) for oral administration and a collar impregnated with a insect growth regulator (IGR). Other novel approaches include parasitic nematodes for outdoor flea control, borate carpet treatments and diatomaceous earth household treatments. It is noted that one of the experts interviewed stated, "Most of the insecticide problems we see are with misapplication.... If you spray your carpet with chlorpyrifos and allow your cat in the room before it dried, the cat may die."

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